Research Square

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Hyper-fractionated radiotherapy bridging CAR-T overcome early relapse for aggressive B-cell CNS lymphoma

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Research Article

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Abstract

Background: Relapsed/refractory (R/R) primary/secondary central nervous system (CNS) lymphoma has poor prognosis and limited treatments. Chimeric antigen receptor T-cell (CAR-T) therapy shows promise but has high early relapse/death rates. Hyper-fractionated radiotherapy (HFRT) enables rapid cytoreduction and immune modulation, potentially enhancing CAR-T efficacy as a bridging approach.

Methods: This prospective pilot study enrolled patients with relapsed or refractory primary or secondary B-cell CNS lymphoma treated at Peking Union Medical College Hospital. All patients received HFRT (30 Gy in 1.5 Gy twice-daily fractions for 10 consecutive days), followed by lymphodepletion and subsequent CAR-T cell infusion. Clinical response, survival outcomes, and toxicities were evaluated according to standard criteria.

Results: 9 R/R CNS lymphoma patients were enrolled. The median follow-up time was 17 (4-34) months after CAR-T infusion. At 1 month follow-up, 6/9 (66.7%) patients achieved complete remission (CR), 1/9 (11.1%) had partial remission (PR) and 1/9 (11.1%) had disease progression (PD) in brain. 7/9 (77.8%) patients had CR at 3 months. 7 patients have been followed up for more than 6 months and remained CR. The 1-year PFS was 87.5% and the 1-year OS was 77.8%. The median PFS and OS were not reached. At Grade ≥3 CRS and ICANS each occurred in one patient (11%). Seven (78%) experienced grade 3–4 myelosuppression, and one patient died of mixed pulmonary infection.

Conclusions: Whole-brain HFRT as bridging strategy helps maintain long-term CAR-T response in CNS lymphoma with favorable safety.

(NCT05514327)

Key points

1. HFRT improved the efficacy and long-term remission of CAR-T by cytoreduction and reverse immune escape with 1-year PFS to be 87.5%.

2. Whole-brain HFRT as a bridging strategy before CAR-T did not increase toxicities including CRS and ICANS.

Background

Relapsed/refractory (R/R) primary or secondary central nervous system (CNS) lymphoma is associated with poor prognosis with few treatment options. Patients with CNS involvement were excluded for CD19 chimeric antigen receptor T-cell therapy (CAR-T) in early trials due to concerns of increased CNS toxicity. However, in recent studies including real-world experience, CAR-T therapy seems to be safe and effective in this population. Nevertheless, most R/R CNS lymphoma patients have rapidly progressive symptomatic disease and bridging treatment is necessary, yet they are often resistant to regular chemotherapies. Furthermore, despite high response rates, higher early relapse or death rates were

observed following CAR-T in CNS lymphoma when compared with other diffuse large B cell lymphoma (DLBCL)(1), which may be due to the special immune microenvironment in CNS.

Radiotherapy could effectively reduce tumors and is a promising bridging strategy for CAR-T in CNS lymphoma. Hyper-fractionated radiotherapy can achieve an effective target dose within a shorter period and minimize radiation damage compared to conventional radiotherapy. Besides, studies in mouse models proved that low-dose radiotherapy may help modify tumor microenvironment to reverse immune escape and to enhance CAR-T cell cytotoxicity. Our center has demonstrated that hyper-fractionated radiotherapy may help improve the overall response rate (ORR) and does not increase the incidence of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) in CAR-T therapy in DLBCL in a pilot prospective study. The value of hyper-fractionated radiotherapy as a bridging strategy in CNS lymphoma is also of great interest to us. In this study, we explored the efficacy and safety of bridging hyper-fractionated radiotherapy in combination with CAR-T therapy for relapsed/refractory primary/secondary CNS lymphoma.

(NCT05514327)

Methods

Patient population

This is a prospectively pilot study. Relapsed/refractory primary/secondary B cell CNS lymphoma patients in Peking Union Medical College Hospital between 2022 and 2025 were enrolled. Written informed consent was signed by each patient. The study was approved by the ethics committee of Peking Union Medical College Hospital and was conducted in accordance with the Declaration of Helsinki.

Treatment and follow-up

Most patients underwent hyper-fractionated radiotherapy after T-cell collection. Whole-brain radiotherapy (WBRT), with inclusion of the orbits in cases with ocular or peri-orbital involvement, was delivered as the primary clinical target volume. Organs at risk, including the lenses and optic nerves, were contoured and dose constraints were applied to minimize radiation-related toxicity. Depending on lesion location and target geometry, intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) was used to improve dose conformity to dominant CNS lesions. A total dose of 30 Gy was prescribed to all patients using a hyper-fractionated regimen of 1.5 Gy twice daily over approximately 10 treatment days (weekends excluded). Dexamethasone was permitted during radiotherapy to control cerebral edema. CAR-T cell infusion was performed 1–2 weeks after the completion of radiotherapy. Adverse reactions at different time points after radiotherapy and CAR-T cell infusion were monitored and analyzed. CRS and ICANS were documented by primary care physicians based on consensus guidelines from the American Society of Transplantation and Cellular Therapy for Cytokine Release Syndrome and

Neurologic Toxicity Associated with Immune Effector Cells. Radiation-related adverse events were graded using Common Terminology Criteria for Adverse Events version 5.0. Enhanced brain MRI and whole body PET/CT were scheduled at 1 month, 3 months, 6 months, 1 year and 2 years to evaluate the disease according to the Lugano criteria. Lumbar puncture was also performed in patients with leptomeninges involvement for efficacy evaluation.

Peripheral blood immune cell subsets were assessed by flow cytometry before and after radiotherapy according to previous protocols(2, 3).

Statistical analysis

Descriptive variables were displayed as percent of all patients with available data while continuous variables were expressed as mean ± SEM. Quantitative data were compared by two-sample (unpaired Student's) two-tailed t test assuming equal variance while categorical data was compared using the Chi-square test. Comparisons among groups were calculated by paired-samples T test. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier survival analysis. A two-sided p value of < 0.05 was considered statistically significant. All the statistical tests were performed using SPSS 21.0 statistical software.

Results

Patient characteristics

From 2022 to 2025, 9 patients were included including 4 primary CNS lymphoma (PCNSL) and 5 secondary DLBCL with CNS involvement (SCNSL). Baseline information is listed in Table 1 with details in Supplementary Table 1. The median age was 55 (40–76) years old and 8 (88.9%) of them were males. 4 (44.4%) were GCB type, 3 (33.3%) were double expressor, 1 (11.1%) had TP53 mutation and 1 (11.1%) was transformed from marginal zone B cell lymphoma. All patients were stage IV at diagnosis according to Ann Arbor stages. 3 (33.3%) patients were primary refractory. The median lines of therapy prior to CAR-T were 3 (2-6lines) and 1 (11.1%) of them had undergone previous autologous stem cell transplantation. 2 (22.2%) patients had lesions outside the brain before radiotherapy. 5 (55.6%) patients had parenchymal diseases, 1 (11.1%) had leptomeningeal diseases, and 3 (33.3%) had both parenchymal and leptomeningeal involvement.

Table 1
basic characteristics of the patients enrolled in our study.

Basic Characteristics	Value
Age at radiotherapy, yr, median(range)	55 (40–76)
Sex, n(%)	
male	8 (88.8%)
female	1 (11.1%)
Disease at diagnosis, n(%)	
PCNSL	4 (44.4%)
Secondary CNS lymphoma	5 (55.6%)
Germinal center type	4 (44.4%)
Double expressor	3 (33.3%)
TP53 mutation	1 (11.1%)
Ann Arbor stage at diagnosis, n(%)	
IV	9 (100%)
Primary refractory disease, n(%)	3 (33.3%)
Lines of therapy prior to CAR-T, n median(range)	3 (2–6)
Prior autologous stem cell transplantation, n(%)	1 (11.1%)
Lesions outside brain before radiotherapy	2 (22.2%)
CNS site involved	
parenchyma	5 (55.6%)
leptomeninges	1 (11.1%)
parenchyma and leptomeninges	3 (33.3%)
CAR-T cell product	
relmacabtagene autoleucel	5 (55.6%)
axicabtagene ciloleucel	4 (44.4%)

Bridging therapy characteristics

All patients received hyper-fractionated radiotherapy with a total dose of 30 Gy delivered as 1.5 Gy twice daily, and all treatment courses were completed within approximately 2 weeks (weekends excluded).

WBRT was administered in all patients; one patient with intraocular involvement received WBRT including both orbits, while the remaining patients received standard WBRT alone. IMRT was used in 3 patients and VMAT in 6 patients based on target geometry. In all cases, at least 95% of the planned gross tumor volume (PGTV) received ≥ 100% of the prescribed dose. 4 (44.4%) patients also received systemic therapy during the bridging period, 3 were BTK inhibitors and 1 was temozolomide. The T-cell collection was performed before WBRT in 7/9 (77.7%) patients, during WBRT in 1 patient and after WBRT in 1 patient. The median time interval between the completion of radiotherapy and CAR-T cell infusion was 12(7–24) days. All patients received fludarabine and cyclophosphamide lymphodepletion before CAR-T cell infusion. 4 (44.4%) received axicabtagene ciloleucel (axi-cel) and 5 (55.6%) received relmacabtagene autoleucel (relma-cel).

Clinical outcomes

Clinical response and survival outcomes

All of them achieved partial response (PR) after the completion of hyper-fractionated radiotherapy and successfully completed CAR-T cell infusion later (Fig. 1). The major target lesion sizes before and after radiotherapy were shown in Supplementary Table 1. The mean reduction in lesion size was 50.7% (16.7%-66.6%). Both leptomeningeal and brain parenchymal lesions responded well to WBRT.

Till submission, the median follow-up time was 17 (4–34) months after CAR-T infusion. At 1 month follow-up, 6/9 (66.7%) patients achieved complete remission (CR), 1/9 (11.1%) had partial remission (PR) and 1/9 (11.1%) had disease progression (PD) in brain. 7/9 (77.8%) patients had CR at 3 months. 7 patients have been followed up for more than 6 months and remained CR (Fig. 2). The 1-year PFS was 87.5% and the 1-year OS was 77.8%. The median PFS and OS were not reached. Of note, the only one patient died of PD had T cell collection during WBRT and the amplification of CAR-T cells in vivo was lower than others. No response or survival differences were found between the patients with or without combined BTKi as bridging therapy and in patients with different CNS site involvement. 2 patients also have systemic involvement before WBRT and CAR-T infusion, 1 with gastric involvement and 1 with lung involvement. One of them achieved CR after CAR-T therapy and the other died of complications within 1 month without efficacy evaluation of lymphoma.

Adverse effects

5 (55.5%) patients experienced grade 1 cytokine release syndrome (CRS), 1 (11.1%) experienced grade 3 CRS, and 3 (33.3%) had no CRS. 2 (22.2%) patients had grade 1 immune effector cell-associated neurotoxicity syndrome (ICANS) and 1 (11.1%) had grade 3 ICANS. Besides, 7 (77.8%) patients experienced grade 3–4 myelosuppression and one of them developed bloodstream infection. 1 patient died of mixed lung infection including covid-19, infuenza A, CMV and aspergillus at 1 month after CAR-T infusion.

Peripheral blood immune cell subsets before and after hyper-fractionated radiotherapy

The absolute number and ratio of peripheral blood immune cell subsets before and after hyper-fractionated radiotherapy were compared. (Supplementary Table 2). Only the ratio of NKT cells (CD3-CD56 + Lym/Lym) was decreased ($p = 0.031$) after radiation while there were no differences between the absolute numbers of all subsets. Interestingly, the only patient who died of PD had a significantly higher ratio and absolute number of CD4 + exhausted cells (PD1 + TIM3 + CD4 + T, 0.91% vs 0.05%, $p < 0.001$), a higher absolute number of Treg cells (CD3 + CD4 + CD25 + CD127-T, 26.7×10^6/L vs 9.7×10^6/L, $p < 0.001$), and especially memory Treg cells (CD45RA-CD3 + CD4 + CD25 + CD127-T, 19.5×10^6/L vs 4×10^6/L, $p = 0.004$) before radiotherapy. After radiation, the total ratio (8.91% vs 0.53%, $p < 0.001$) and absolute number of exhausted T cells (PD1 + TIM3 + T, 64.3×10^6/L vs 2.9×10^6/L, $p < 0.001$) including CD4 + and CD8 + exhausted T cells were still significantly higher in this patient than in others. We also found a significantly higher ratio (3.34% vs 0.48%, $p = 0.022$) and absolute number (19.2×10^6/L vs 2.9×10^6/L, $p = 0.049$) of nonclassical monocytes (CD14-CD16++) in this patient before CAR-T cell infusion. (Fig. 3)

Discussion

Relapsed or refractory primary or secondary CNS lymphoma remains one of the most challenging scenarios in aggressive B-cell lymphomas(4). The median OS of R/R CNSL patients is around 6 months after relapse with limited treatment strategies(5). CAR-T therapy is one of the major improvements developed in recent years in the management of systemic DLBCL. CNS lymphomas were excluded in early trials because of poor prognosis and fear of neurotoxicity. With cases reported in real-world, the potential role of CAR-T in treating CNS lymphomas was confirmed, although early relapse and neurotoxicity still limit outcomes (6–9). In our prospective pilot study, we explored hyper-fractionated whole-brain radiotherapy (HFRT) as a bridging strategy prior to CAR-T and observed high response rates, durable remissions, and acceptable safety, suggesting that HFRT may optimize the therapeutic window of CAR-T in CNS lymphoma.

Compared with historical studies of CAR-T, our cohort achieved higher response rates and more sustained remissions. In prior reports, CR rates after CAR-T for CNS lymphoma typically ranged from 30%–60% and median PFS was 3-6months (5, 10–12). Cook, M.R et al. meta-analyzed 128 CNS lymphoma patients and found CR rates of 56% (PCNSL) and 47% (SCNSL), with 6-month CR rates of 37% in both groups(13). The second meta-analysis included 141 patients from 19 studies showed the ORR and CR rated were 61% and 55%, the median OS was 8.8 months and the median PFS was 4.4 months(14). As for large retrospective studies, one multicenter retrospective cohort study in US including 61 patients revealed that the overall response rate was 68% while the median PFS was only 3.3 months (2.6-6 months) and the 1-year PFS rate was 35% in SCNSL who received CAR-T therapy(15). Another retrospective analysis of 89 patients (11 PCNSL and 78 SCNSL) performed by the EBMT lymphoma working party and the GoCART Coalition indicated a 37% OS and 30% PFS at 24 months(16).

Among these patients, bridging therapy is mostly used in patients with aggressive disease or high tumor burden while lack of detailed information in most retrospective studies. In our study, the CR rate was 77.9% at 3 months, the 1-year PFS was 87.5% and the 1-year OS was 77.8%, better than previous reports. These favorable outcomes support the hypothesis that effective disease debulking before CAR-T infusion reduces early relapse and improves CAR-T engagement(17, 18). Radiotherapy is particularly advantageous as a bridging modality for CNS lymphoma because it provides rapid successful cytoreduction. A small cohort conducted by Cederquist, G.Y et al demonstrated successful rapid cytoreduction by bridging CNS radiotherapy before CAR-T and is associated with a favorable CNS response and safety profile, the best ORR was 9/12 (75%) and 3 patients experienced CNS relapse within 1 year who all had leptomeningeal involvement(19). Recently, Shi, H reported a retrospective study with 27 CNS lymphoma received WBRT as bridging therapy, the ORR reached 88.9% and the 1-year estimated PFS and OS rate were 61.3% and 56.6%, demonstrates WBRT as a promising bridging strategy for CAR-T in CNS lymphoma.

Beyond the general advantages of radiotherapy, our use of hyper-fractionated WBRT provides additional biological and clinical benefits. Hyperfractionation, characterized by smaller doses delivered twice daily, is commonly used in rapidly progressive tumors and has been retrospectively shown to be effective and safe as salvage therapy for CNS lymphoma and as consolidation after hematopoietic stem cell transplantation(20, 21). In our study, we applied 30 Gy in 20 twice-daily fractions over only 10 days as bridging prior to CAR-T therapy. Compared with conventional WBRT regimens (40–50 Gy over several weeks), this schedule markedly shortened treatment duration and accelerated cytoreduction, while minimizing the risk of late neurocognitive toxicity. Furthermore, hyper-fractionated low-dose radiation may enhance CAR-T efficacy by remodeling the immune microenvironment (22), which are particularly relevant in the CNS where immune privilege and T-cell exhaustion often limit systemic therapies(23, 24). In our study, we also found higher exhausted total T cells (PD1 + TIM3 + T)and nonclassical monocytes before CAR-T infusion may indicate worse prognosis. Compared with traditionally high doses, low-dose radiation can facilitate antitumoral Th1 immune response(25) and reduce immunosuppressive cytokines such as TGF-β and IL-10(26). It also promotes M2 type macrophage skewing (27) and reduces Treg cells(26, 28) in vivo studies. Our study showed that total exhausted T cells and nonclassical monocytes tended to decrease; yet, no significant differences were observed, likely due to the relatively small sample size. Preclinical models in recent years demonstrated that low-dose radiotherapy reverses tumor immune desertification and resistance to immunotherapy(29) and is a promising strategy to prime responses to checkpoint blockade(30). Furthermore, low dose radiation also increases antigen presentation, upregulates adhesion molecules (e.g., ICAM-1) and chemokines, facilitating CAR-T cell trafficking across the blood-brain barrier into the tumor microenvironment(31–34). These mechanisms may contribute to the PFS and OS advantages in our cohort.

Safety is a major concern in CNS-directed CAR-T therapy due to the risk of CRS and ICANS in the early years. However, recent studies have fully confirmed the safety in this population, including those who received radiotherapy as a bridging treatment(13, 14). Our study also addressed with a favorable toxicity

profile: grade ≥ 3 CRS (11.1%) and ICANS (11.1%). Notably, leptomeningeal involvement, a known risk factor for ICANS, was present in 44.4% of our patients, yet toxicity remained manageable.

This study has limitations. The sample size was small (n = 9) and the median follow-up time was relatively short (17 months), limiting the ability to assess long-term efficacy and late toxicities. Lymphoma subtypes (PCNSL vs SCNSL) and CAR-T products (axi-cel vs relma-cel) were heterogeneous, which may have affected outcomes. Control groups were not included, preventing direct comparison with other strategies such as chemotherapy or conventional WBRT schedules. Mechanistic analyses, including immune profiling and CAR-T persistence in cerebrospinal fluid, are ongoing and will be essential to understand how HFRT modulates the CNS microenvironment. Future multicenter prospective trials with larger cohorts and molecular stratification (e.g., TP53 mutation, germinal center subtype) are warranted to validate these findings.

In conclusion, hyper-fractionated WBRT as a bridging strategy enhances the efficacy of CAR-T therapy in CNS lymphoma while maintaining a favorable safety profile. By combining rapid cytoreduction with potential immune modulation, HFRT helps maintain long term response and address key barriers to successful CAR-T treatment in the CNS lymphoma. As CAR-T therapy moves to earlier lines of treatment, HFRT bridging should be further investigated in larger cohorts and mechanical studies to define its role in curative strategies.

Declarations

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Conflict of Interest:

The authors declare no conflict of interests.

Authors' contribution:

R.J., Z.W., Z.D.B., H.X.R. and Z.F.Q. designed the study. Z.Y., Z.D.Q., W.C., H.K., Z.W., H.X.R. helped to collect clinical data and provide critical suggestions. Material preparation and data analysis were performed by R.J. and Y.Y.Y. The first draft of the manuscript was written by R.J. and Y.Y.Y. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability statement:

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1

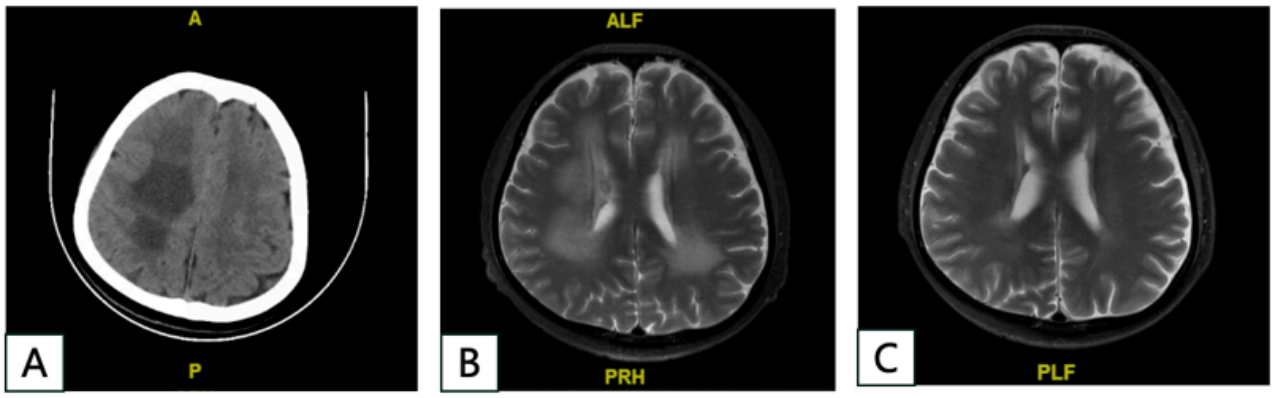


Figure 1

A case of CNS lesion. A) baseline CT showed multiple tumor lesions with peripheral edema, the diameter of maximal lesion was 1.5cm. B) after radiotherapy the tumor lesions shrank, the maximal lesion shrank to 0.74cm with ring-like enhancement. C) after CAR-T cell infusion at 1 month, the lesions disappeared.

Figure 2

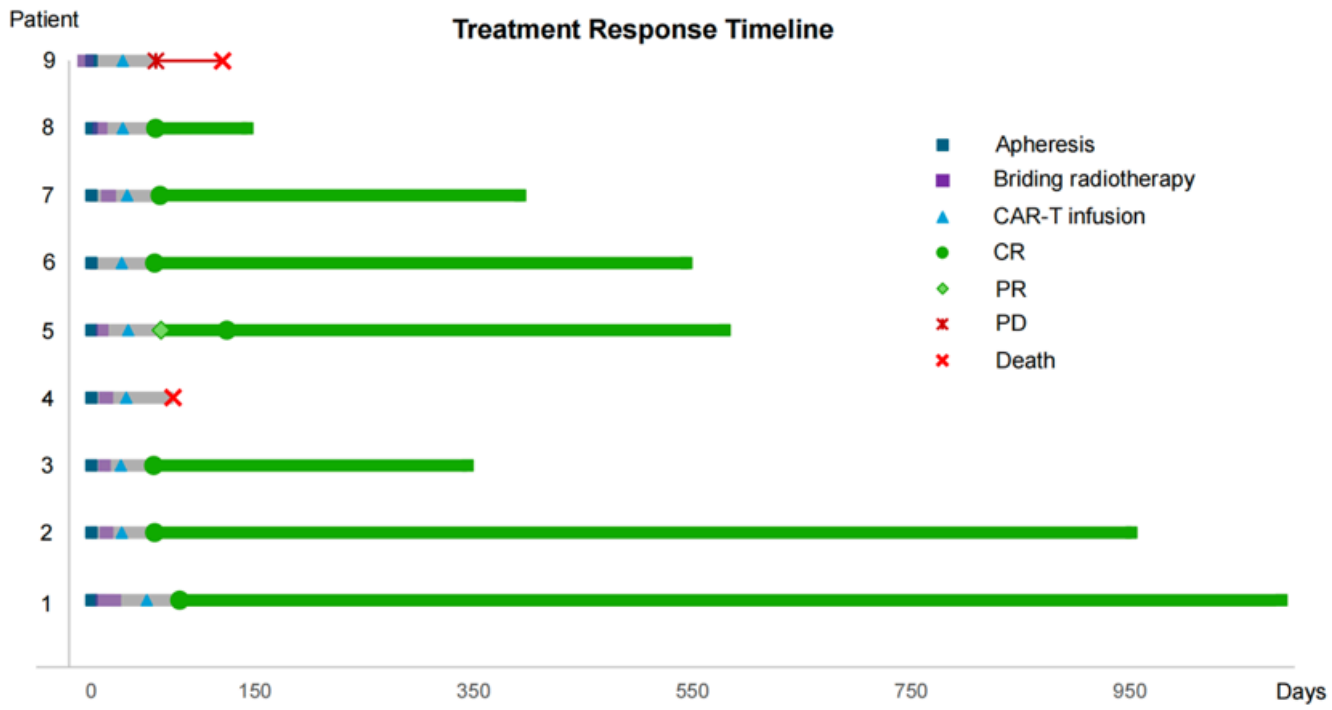


Figure 2

Swimmers plot of treatment, response, and relapse time for 9 patients with CNSL. Status and events are coded in the legend.

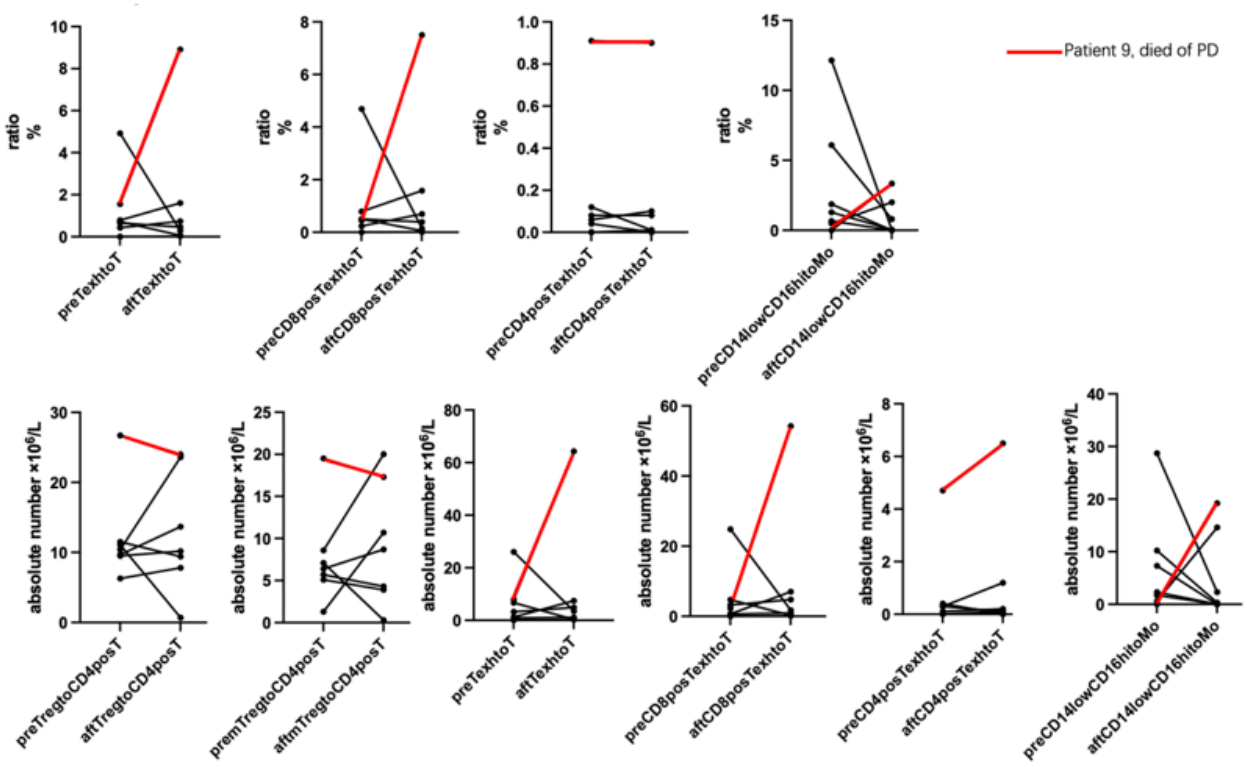


Figure 3

The peripheral blood immune subsets before and after HFRT. The only patient who died of PD had a significantly higher ratio and absolute number of CD4+ exhausted cells, and a higher absolute number of Treg cells before radiotherapy. After radiation, the total ratio and absolute number of exhausted T cells and nonclassical monocytes were higher than others.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx
- SupplementaryTable2.xlsx